GlaxoWellcome

October 6, 1998

DESK COPY

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, Woodmont II, Room 4037
1451 Rockville Pike
Rockville, MD 20852

Re: NDA 20-241/S-003; LAMICTAL® (lamotrigine) Tablets
NDA 20-764/S-001; LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets
Amendment to Pending Application: Labeling

Dear Dr. Leber:

Reference is made to a teleconference held on October 2, 1998 between members of the Division and Glaxo Wellcome Inc. regarding proposed labeling submitted on April 15, 1998 and September 9, 1998 for the aforementioned applications.

Appended is revised proposed labeling and a rationale for the proposed changes which addresses the Agency's comments from the October 2, 1998 teleconference. The following changes have been made to the proposed labeling:

DOSAGE AND ADMINISTRATION

- Conversion to LAMICTAL monotherapy from an enzyme-inducing AED (EIAED)
 and from valproate are discussed separately. Recommendations for conversion from
 an EIAED to LAMICTAL monotherapy are based on the conversion scheme used in
 the pivotal trial (US 30/31).
- Inclusion of a statement that there is no experience in converting patients from valproic acid to LAMICTAL monotherapy and that no specific guidelines can be offered at this time. The known pharmacokinetic interaction between LAMICTAL and valproic acid are also detailed in this section.
- We propose that the recommendations for initial monotherapy as outlined in the DOSAGE and ADMINISTRTION section remain the same.

Paul D. Leber, M.D. October 6, 1998 Page 2

INFORMATION FOR THE PATIENT

• Revision of the "How to Use LAMICTAL" section to state that the dose of LAMICTAL should be increased slowly rather than added slowly to reflect patients who may be receiving LAMICTAL as initial monotherapy.

This submission consists of the following:

Attachment 1 contains a rationale for the proposed changes to labeling.

Attachment 2 contains proposed labeling with additions underlined and deletions noted with strike-throughs. The base labeling is that which was submitted to NDA 20-764/S-001 (LAMICTAL Chewable Dispersible Tablets) on September 9, 1998.

Attachment 3 contains a clean, unannotated copy of proposed labeling.

This labeling is being submitted to NDA 20-241/S-003 and incorporated by reference to NDA 20-764/S-001. A desk copy of this submission is being provided to Jacqueline Ware, Pharm.D., Regulatory Management Officer, under separate cover.

Reference is also made to the Agency's request for additional information regarding clinical data from US 17 and US 26, which was submitted in support of the safety of the LAMICTAL 500 mg/day monotherapy dose. A response to this request will be sent under separate cover as soon as the additional information is available.

We are available at your convenience to discuss this submission. If you have any questions regarding this submission, please do not hesitate to contact me at 919-483-6466.

Sincerely,

Elizabeth A. McConnell, Pharm.D.

Elizabete Mcconnell

Project Director

Regulatory Affairs

Cc: Jacqueline Ware, Pharm.D., Regulatory Management Officer, HFD-120

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338. Expiration Date: April 30, 2000. See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

NAME OF APPLICANT	a language	DATE OF SUBMISSION				
Glaxo Wellcome Inc.		October 6, 1998				
TELEPHONE NO. (Include Area Code)		FACSIMILE (F	AX) Number (Include Area Code)			
(919) 483-2100		(919)	483-5063			
APPLICANT ADDRESS (Number, Street, City, State, Co and U.S. License number if previously issued): Five Moore Drive Research Triangle Park, NC 27709	ountry, ZIP Code or Mail Code		AGENT NAME & ADDRESS (Number, Street, City, St & FAX number) IF APPLICABLE			
PRODUCT DESCRIPTION			<u> </u>			
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER	OR BIOLOGICS LICENSE AF	PPLICATION NUMBER (if p	previously issued) 20-241			
ESTABLISHED NAME (e.g., Proper name, USP/USAN I	name)	PROPRIETARY NAME (b) Lamictal® Ta				
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME 3,5-diamino-6-(2,3-dichlorophenyl)-	The control of the co		CODE NAME (If any) BW430C			
DOSAGE FORM:	STRENGTHS:		ROUTE OF ADMINISTRATION:			
Tablets	25mg, 100m	g, 150mg, 200mg	Oral			
(PROPOSED) INDICATION(S) FOR USE Adjunctive treatment of partial seizu	ires in adults with epil	epsy				
APPLICATION INFORMATION						
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NDA 20-241/S-003 LAMICTAL® (lamotrigine) Tablets NDA 20-764/S-001 LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

Rationale for Proposed Labeling Revisions: Monotherapy

General comments:

- There is a linear relationship between LAMICTAL doses and lamotrigine plasma concentrations.
- The effects of EIAEDs and VPA on LAMICTAL pharmacokinetics are well established.
- A "monotherapy-equivalent dose" is defined as (1) one-half the LAMICTAL dose
 used with concomitant EIAED or (2) twice the LAMICTAL dose used with
 concomitant VPA.
- Based on serum concentration data from US 26 and US 17 and dosing data from US 30/31, there is considerable experience at "monotherapy-equivalent" doses of LAMICTAL at 500 mg/day or higher. A total of 503 patients in these two studies received doses \geq 500 mg/day, of which 297 were exposed for at least 6 months, and a total of 306 patients received doses \geq 700 mg/day, of which 197 were exposed for at least 6 months.
- The currently approved LAMICTAL package insert provides for an 8-week titration
 to "monotherapy-equivalent" doses of 400 mg/day LAMICTAL for patients taking
 concomitant VPA. Thus, the only gap in direct clinical experience is that between
 400 and 500 mg/day.
- The proposed titration rate for escalating initial monotherapy with LAMICTAL from 400 mg/day to 500 mg/day is less than or equal to rates (of predicted serum concentrations) already approved for adjunctive therapy with LAMICTAL and concomitant VPA.
- All of the currently approved dosing schedules use rates that are relatively slow during the first 4-weeks and then allow a slight increase in rate thereafter. None of the proposed monotherapy dosing schedules exceeds the escalation rates associated with currently approved schedules.
- We offer no dosing guidelines for conversion to monotherapy with LAMICTAL in patients receiving more than one concomitant AED.

Rationale for dosing guidelines for "Conversion from a concomitant EIAED to monotherapy with LAMICTAL".

Comment: The Agency expressed a concern about the rate of rise of lamotrigine plasma levels during taper and after discontinuation of the EIAED.

Response: As seen in US 30/31, average plasma concentrations of lamotrigine increased from approximately 4 ug/ml to approximately 8 ug/ml over an 8-week period after the complete withdrawal of the EIAED. This rate of increase (0.5 ug/ml/week) is equal to or less than the rate observed using currently approved dosing guidelines regardless of concomitant AED.

Rationale for dosing guidelines for "Conversion from concomitant VPA to monotherapy with LAMICTAL"

Comment: The Agency expressed a concern about the manner in which under- or over-dosing of LAMICTAL relative to the currently approved dose of LAMICTAL with concomitant VPAcould be avoided following the withdrawal of VPA.

Response: Although the effect of the withdrawal of VPA on lamotrigine serum concentrations is known, the rate at which this effect occurs has not been characterized. As described in the currently approved "Clinical Pharmacology Section", discontinuation of concomitant VPA will result in a halving of lamotrigine plasma concentrations, suggesting a doubling of the LAMICTAL dose would be required to compensate for the loss of VPA's inhibitory effect. We believe it is important to remind the prescribing physician of this pharmacokinetic interaction in the DOSAGE AND ADMINISTRATION section, even though we cannot currently offer specific dosing guidelines for this group of patients.

Rationale for dosing guidelines for "Initial monotherapy in patients > 16 years of age"

Comment: The Agency expressed concerns that the titration phase would be too long if the slowest schedule, that for patients taking concomitant VPA, was used.

Response The proposed dosing schedule for initial monotherapy, which achieves 500 mg/day within 9 weeks, is associated with essentially the same rate of increase in lamotrigine serum concentrations as that seen when the VPA guidelines are used. The safety of the proposed initial monotherapy dosing schedule is based on data in over 400 patients who titrated to a maximum dose of 200 mg/day. Although there are no specific safety data in patients using this titration schedule to achieve monotherapy doses above 200 mg/day, it should be noted that patients taking LAMICTAL 200 mg/day with concomitant VPA in reality experience the pharmacokinetic equivalence of LAMICTAL 400 mg/day as monotherapy. It should be also be noted that these patients have lamotrigine serum concentrations of by Week 6. Thus, the only gap in clinical experience is that between 400 and 500 mg/day. However, since the risk of rash is

greatest in the first 2 to 8 weeks of initiation of LAMICTAL treatment, use of this scheduled is justified.

APPEARS THIS WAY

GlaxoWellcome

July 25, 1997

Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, Woodmont II, Room 4037
1451 Rockville Pike
Rockville, MD 20852



Re: NDA 20-241; LAMICTAL® (lamotrigine) Tablets
Amendment to Pending Application: Revised Labeling for Supplement 003

Dear Dr. Leber:

Reference is made to correspondence dated December 17, 1996 in which the Agency requested a boxed warning for NDA 20-241, LAMICTAL Tablets, which discusses the risk of serious rash associated with the use of LAMICTAL in adults and children with epilepsy. Wording for the boxed warning and associated changes to the labeling for NDA 20-241 was approved on March 11, 1997.

At this time, we are providing revised labeling for the aforementioned supplemental application (submitted to FDA on February 24, 1997) which incorporates the boxed warning requested by the Agency on December 17, 1996 and approved on March 11, 1997. Differences from the proposed labeling sent with the supplemental application, in particular the change in the proposed minimum age from 13 to 16 years, are specified in the annotated copy. Desk copies of this submission are being provided to John Feeney, M.D., Reviewing Medical Officer, and Jacqueline Ware, Pharm.D., Regulatory Management Officer under separate cover. Diskettes containing an electronic copy of the revised label (unannotated and without revision marks) in Word for Windows format are provided in the archival copy and the desk copies for Drs. Feeney and Ware.

Paul D. Leber, M.D. July 25, 1997 Page 2

If you have any questions regarding this submission, please do not hesitate to contact me at 919-483-6466.

Sincerely,

Elizabeth A. McConnell, Pharm.D.

Elizabeth McConnell

Project Director Regulatory Affairs APPEARS THIS WAY
ON ORIGINAL

cc: John Feeney, M.D., Reviewing Medical Officer, HFD-120
Jacqueline Ware, Pharm.D., Regulatory Management Officer, HFD-120

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338. Expiration Date: April 30, 2000. See OMB Statement on last page.

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Lamiotrigine CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine DOSAGE FORM: Tablets STRENGTHS: 25mg, 100mg, 150mg, 200mg PROPOSED INDICATION(S) FOR USE Adjunctive treatment of partial seizures in adults with epilepsy APPLICATION INFORMATION BIOLOGICS LICENSE APPLICATION (21 CFR 314.50) BIOLOGICS LICENSE APPLICATION (21 CFR part 601) F AN NDA, IDENTIFY THE APPROPRIATE TYPE SO5 (b) (1) SO5 (b) (2) FAN NDA, IDENTIFY THE APPROPRIATE TYPE SO5 (b) (1) SO5 (b) (2) FAN NDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Holder of Approved Application PRESUBMISSION PRESUBMISSION ANNUAL REPORT BESTABLISHMENT DO A PENDING AND CONTROLS SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OVER THE COUNTER PRODUCT (OTC) UMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS X PAPER PAPER AND ELECTRONIC	(Title 21, Code of Federal Regulations, 314 & 601) APPLICANT INFORMATION NAME OF APPLICANT Glaxo Wellcome Inc. TELEPHONE NO. (Include Area Code) (919) 483-2100 APPLICANT ADDRESS (Number, Street, City, State, Counter, 710 Oct to Maria	FACSIMILE (FACSIMILE (FACSIMILE) (P19) 4	BMISSION 5, 1997 AX) Number (Include Area Code)			
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Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current

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		A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2) B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)							
		C. Methods Validation Package (e.g. 21	CER 314 50 (a) (3) (i) 24	y upon FDA's requ	est)	<u> </u>			
	5.								
	6.								
_	7.	Human pharmacokinetics and bioavailabili Clinical Microbiology (21 CFR 314.50 (d) ((d) (3) , 21 CFR 6	301.2)				
_	8.	Clinical data section (21 CFR 314.50 (d) (
	9.								
+		Statistical section (21 CFR 314.50 (d) (6),							
-		Case report tabulations (21 CFR 314.50 (f							
-		Case reports forms (21 CFR 314.50 (f) (2)							
		Patent information on any patent which cla			Alle Deserve				
	14.	A patent certification with respect to any pa	atent which claims the dru	g (21 U.S.C. 355 (t	o) (2) or (j) (2) (A))				
-		Establishment description (21 CFR Part 60			elia de la companya della companya d				
		Debarment certification (FD&C Act 306 (k)							
		Field copy certification (21 CFR 314.5 (K) ((3))						
_		User Fee Cover Sheet (Form FDA 3397)		Alle site editions of Health					
	19.	OTHER (Specify)							
his apoduct	3. L. 4. Ir 5. R 6. R 7. Lopplic t unti	update this application with new safety in precautions, or adverse reactions in the d by FDA. If this application is approved, I apply that it is apply that it is approved, I apply that it is apply that it is approved, I apply that it is appl	R Part 600. 0, 660 and/or 809. product, prescription drug on in 21 CFR 314.70, 314. 4.81, 600.80 and 600.81. ct laws. as proposed for scheduling ces a final scheduling decis	advertising regulat 71, 314.72, 314.97, under the Controll sion.	tions in 21 CFR 20, 314.99 and 601.	02. 12.			
NATI	URE	OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	tion 1001.	<u> </u>				
lu	40	best micanual	Elizabeth A. M	cConnell, Pharr	n.D.	July 25, 1997			
	Δ.	Street, City, State, and ZIP Code)	Project Directo	r, Regulatory A	ffairs				
Fi	ve N	Moore Drive			Telephone	Number			
Re	esea	arch Triangle Park, NC 27709			(91	9) 483-6466			
truction truction truction tructing	ions, tion. g this	orting burden for this collection of info, searching existing data sources, gather Send comments regarding this burden is burden to:	ormation is estimated to ring and maintaining the estimate or any other as	average 40 hours data needed, ar spect of this colle	per response, in nd completing ar ection of informat	cluding the time for review of reviewing the collection ion, including suggestions			
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DEPARTMENT OF HEALTH & HUMAN SERVICES





Food and Drug Administration Rockville MD 20857

NDA 20-241/S-003 NDA 20-764/S-001

Glaxo Wellcome Inc.

Attention: Elizabeth A. McConnell, Pharm.D.

Project Director, Regulatory Affairs

Five Moore Drive P.O. Box 13398

Research Triangle Park, NC 27709

OCT 1 6 1998

Dear Dr. McConnell:

Please refer to your supplemental new drug applications dated February 24, 1997 (NDA 20-241/S-003), and September 4, 1998 (NDA 20-764/S-001), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamictal (lamotrigine) Tablets and Lamictal (lamotrigine) Chewable Dispersible Tablets.

We acknowledge receipt of your additional correspondence and amendments to these supplemental applications dated:

NDA 20-241/	S-003 only Roth Application	
February 24, 1998	July 16, 1000	
April 15, 1998	Assessed 21 1000	
June 10, 1998	August 21, 1998 October 9, 1998	

June 10, 1998

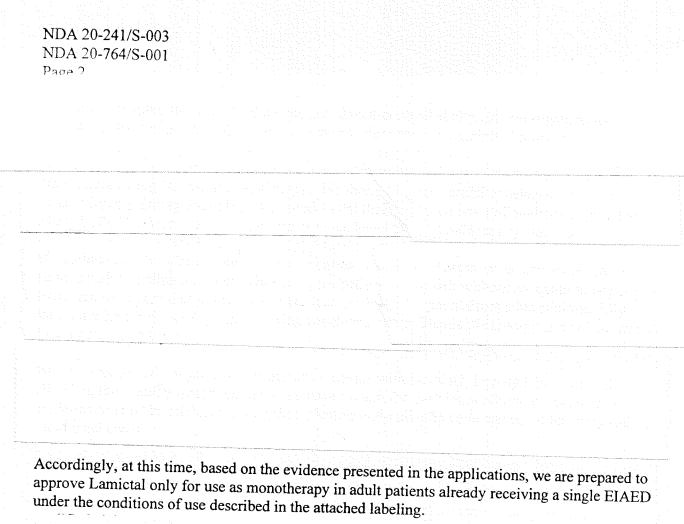
July 2, 1998

September 9, 1998 October 1, 1998

The user fee goal date for NDA 20-241/S-003 is October 17, 1998. The user fee goal date for NDA 20-764/S-001 is September 8, 1999.

These supplemental new drug applications are intended to allow for the use of Lamictal (lamotrigine) Tablets and Lamictal (lamotrigine) Chewable Dispersible Tablets as monotherapy for partial seizures in adults with epilepsy.

We have completed the review of these applications, as amended, and have concluded that they are approvable, provided that the products are marketed under labeling that is essentially identical, save for minor editorial changes, to that attached to this letter.



Although sections of this or have been deleted.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

NDA 20-241/S-003 NDA 20-764/S-001 Page 3

APPEARS THIS WAY

ON ORIGINAL

If you have any questions, contact Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-5793.

Sincerety yours,

Paul Leber, M.D.

Director

Division of Neuropharmacological

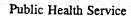
Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES





Food and Drug Administration Rockville MD 20857

NDA 20-241/S-003

Glaxo Wellcome, Inc.

Attention: Elizabeth A. McConnell, Pharm.D.

Five Moore Drive; P.O. Box 13398 Research Triangle Park, NC 27709 FEB 2.4 1998

Dear Dr. McConnell:

Please refer to your supplemental new drug application dated February 24, 1997, received February 25, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamictal (lamotrigine) Tablets, 25mg, 50mg, 100mg, 150mg, 200mg, and 250mg.

We acknowledge receipt of your additional correspondence and amendments to the NDA dated:

June 6, 1997 July 25, 1997 September 4, 1997 September 15, 1997

December 16, 1997 December 23, 1997

The User Fee goal date for this application is February 25, 1998.

This supplemental application provides for the expansion of the indication to include the use of Lamictal as monotherapy of partial seizures in adults with epilepsy.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to respond to the following requests or comments.

Labeling

The attachment to this letter provides a draft of the labeling that the Agency asks you to adopt for Lamictal Tablets upon approval of this application. Although sections of this proposal are taken verbatim from the labeling proposed by you, other sections have been revised. Please note that we have embedded throughout the text of the attached draft labeling, "Notes to Sponsor:", requesting further revisions or clarification of the label.

Please amend your February 24, 1998 response with consolidated labeling which incorporates labeling changes from this letter.

Lastly, to facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Safety Issues

We have a number of requests regarding the presentation of safety data.

1. Sudden Unexplained Deaths

Please present the data for all Sudden Unexplained Deaths in Epilepsy (SUDEs) with appropriate patient time exposure data for the monotherapy experience. Please express the rate as number of SUDEs/patient-year.

2. Serious Dermatologic Events

It has been difficult to obtain a clear picture of the number and type of serious rashes that have occurred in this population. Please submit a comprehensive report of all rash, with an emphasis on serious rash; the latter should be defined as had previously been agreed to in our discussions regarding the supplement for Lennox-Gastaut. This report should make clear the incidence of these events for separate cohorts; for patients in the development program, you should make clear which of these patients were still receiving concomitant AEDs and which patients were on true monotherapy. The total exposure under each of these conditions, including patient time, should be presented. Please also submit any post-marketing reports of serious rash in patients receiving monotherapy, with any information about use as monotherapy, if available.

In addition, for cases seen in the development program, you should present controlled trial data separately from that obtained in open, uncontrolled settings.

3. Other Adverse Events

We recognize that your draft label presents adverse event data for the Transition Phase and the Monotherapy Phase separately. It has been difficult to find this separate presentation in your NDA. If you have submitted this in your application, please inform us where it is located. If you have not, please submit such a presentation and analysis.

NDA 20-241/S-003 Page 3

Please understand that the draft labeling may need to be further revised based on your answers to the above comments.

Safety Update

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

- Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted <u>vs</u> now will certainly facilitate review.
- 2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.
- 3. Provide details of any significant changes or findings, if any.
- 4. Summarize worldwide experience on the safety of this drug.
- 5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

Promotional Material

Please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-241/S-003 Page 4

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

If you have any questions, please contact Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-2850.

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APPEARS THIS WAY
ON ORIGINAL

/S/ _ 2/24/98

Sincerely yours,

Paul Leber, M.D.

Director

Division of Neuropharmacological Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL